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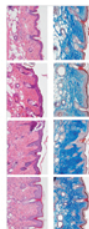
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REVIEW

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Unmasking sarcoidosis following surgery for Cushing disease

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ABSTRACT

We present a patient with Cushing disease apparently suppressing sarcoidosis, which was unmasked following surgical resection of a pituitary adrenocorticotropin (ACTH)-producing microadenoma. Case report and a short review of the literature published in this area. A 46-year-old Caucasian woman presented with symptoms of hypercortisolism such as progressive weight gain, Cushingoid appearance, proximal myopathy, easy bruising, and amenorrhea. Blood testing including inferior petrosal sinus sampling uncovered an ACTH-producing microadenoma in the right aspect of the anterior pituitary gland for which the patient underwent transphenoidal resection. Maintenance corticosteroid therapy was implemented, and the signs and symptoms of Cushing disease began to resolve. Three months after surgery, multiple erythematous painful nodules developed on the patient's arms. Erythema nodosum (EN) was diagnosed clinically and a suspicion of underlying sarcoidosis was substantiated by lung imaging and elevated plasma interleukin (IL)-2 receptor. One month later, the lesions spontaneously resolved without therapy other than maintenance glucocorticoid replacement. Physicians should be aware that patients undergoing successful treatment of Cushing syndrome may have a flare-up or emergence of a corticosteroid-responsive disease.

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Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. Typical presentations of this disease relate to the lungs (dry cough), the eyes (anterior uveitis) or the skin (EN or cutaneous sarcoidosis). EN is characterized by inflammatory, red nodules that are usually tender, multiple, and bilateral. The nodules typically erupt on the shins but may also be seen on the thighs, trunk or upper extremities.

Cushing disease is characterized by an ACTH-dependent hypercortisolism which manifests itself as Cushing syndrome. Signs of Cushing syndrome include upper body obesity (moon face, buffalo hump, abdominal fat distribution), striae, wasting of the limbs and excess body fluid. The long-term complications of hypercortisolism are significant and include osteoporosis, hypertension, diabetes mellitus, hirsutism, and amenorrhea.^{1,2}

Here, we report a rare case of a patient who presented with EN on the upper extremities a few months after surgically induced remission of Cushing disease. She was diagnosed with sarcoidosis.

Case Presentation

In August 2011, a 45-y old Caucasian woman of Scandinavian descent was referred to our tertiary referral center on suspicion of Cushing syndrome after urinary-sis had documented elevated 24-h urinary excretions of cortisol (1231–1711 nmol/24h, normal range <340).

Prior to referral the patient had a two-year history with a multitude of symptoms including fatigue, altered fat distribution, difficulty climbing stairs (possible sign of myopathy), and an unintended weight gain of 10 kg (BMI 28.4), easy bruising, increased hair growth on the face and extremities, and amenorrhea. No hyperpigmentation was noted. Prior medical history was otherwise uneventful.

Suspicion of ACTH-dependent Cushing syndrome was confirmed with a low-dose dexamethasone suppression test which showed a lack of cortisol suppression (plasma cortisol 563 nmol/L, reference range <50) and elevated plasma ACTH (15 pmol/L, reference range <10). A corticotropin-releasing hormone stimulation test demonstrated clear increases of both plasma ACTH and cortisol

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peak levels (45 pmol/L and 982 nmol/L respectively) suggestive of Cushing disease. A gadolinium-enhanced high-resolution pituitary MR did not detect a tumor, but inferior petrosal sinus sampling provided evidence of pituitary ACTH hypersecretion with significantly higher values obtained from the right sinus.

Transsphenoidal exploration on the right side of the pituitary gland revealed a microadenoma which was removed. After surgery hypocortisolism was detected and the patient started substitution with hydrocortisone. The pathology report showed a pituitary adenoma with ACTH positivity.

Outpatient follow-up was uneventful. The patient lost 8 kg (BMI 22.4) and reconstituted completely from the clinical stigmata of Cushing syndrome including hirsutism which began to resolve one month after surgery. She still experienced some fatigue, but at a self-reported lower level.

Three months after surgery the patient experienced an eruption of multiple painful red nodules distributed symmetrically on both arms (**Fig. 1**). The lesions were consistent with a resolving panniculitis with overlying blanchable erythema, which was slightly raised above the surrounding skin. The eruption was clinically diagnosed as EN and faded slowly over the next two months without treatment (**Fig. 2**). A



Figure 1. Erythema nodosum with bilateral eruption of painful subcutaneous nodules with overlying inflammatory redness. Involvement of only the upper extremities is unusual.

systematic review of other organ systems elicited no further complaints such as fever, conjunctivitis, dyspnea, arthralgias or gastrointestinal symptoms. A chest radiograph and subsequent chest CT scan unveiled bilateral hilar lymphadenopathy. Blood tests revealed elevated levels of IL-2 receptor (1010 kU/L, normal range 223–710). All other inflammatory parameters including erythrocyte sedimentation rate, C-reactive protein, and lymphocytes were normal. Levels of angiotensin converting enzyme, calcium, vitamin D, and immunoglobulins were normal, as was tuberculosis testing.

Lung function tests including diffusion capacity as well as an ECG were normal. The diagnosis of sarcoidosis was made based on radiological findings, IL-2 receptor levels, and the eruption of EN. Additional pathology work-up of the pituitary microadenoma excluded neurosarcoidosis of the pituitary gland.

Discussion

The findings of bilateral hilar adenopathy on chest imaging is highly suggestive of grade 1 sarcoidosis. Important differential diagnoses such as tuberculosis and malignancy were excluded. EN and an elevated IL-2 receptor level further supports the diagnosis of sarcoidosis, although they are neither sensitive nor specific for sarcoidosis.³ Testing for hepatitis C or yersiniosis was not found relevant in the clinical setting. In conjunction with the patient it was decided not to perform lung and skin biopsies as her lung involvement was mild and her skin lesions were resolving. Of special note, the clinical and paraclinical features did not suggest vasculitis.

The disease manifestations of sarcoidosis were most probably demasked after definitive treatment



Figure 2. Two months after the initial skin eruption. Clinical examination revealed only residual discoloration and slight induration.

for Cushing disease by transsphenoidal adenectomy. The eruption of EN in an atypical location became a clue to the diagnosis. Alternatively the sarcoidosis could be part of a rebound phenomenon of autoimmunity presenting after cessation of a prolonged period of hypercortisolism as recently described by da Mota.⁴ Finally it could also be a coincidence.

A review of the literature (MeSH-terms “Cushing syndrome” AND “Sarcoidosis”; limits: humans, all languages, 1970–2014) revealed only five similar case reports.^{1,2,5–9} Only one of these describes a similar case of EN as the presenting sign of underlying sarcoidosis.^{3,6}

Taking a broader view of hypercortisolic states the study by da Mota et al.⁴ pooled 11 case reports of overt immune dysfunction following remission of Cushing syndrome. Another study even coined the term “Cushing cure syndrome” to highlight the immunologic aftermath of supposed cure.¹⁰ In the study by da Mota overt autoimmune and allergic diseases such as psoriasis, sarcoidosis, Graves’ disease, autoimmune thyroiditis, eczema and asthma were diagnosed in 11 of 66 patients (16.7%) who achieved remission of Cushing syndrome. In eight patients (73%) symptoms were noted for the first time, and in three patients (27%) symptoms were exacerbated after remission. Of note, the female to male ratio was 6:1.

It is interesting to speculate that enhanced ACTH (and other melanocortin peptides like proopiomelanocortin or α -melanocyte-stimulating hormone) in addition to increased cortisol levels may have contributed to mask the skin inflammation by affecting the immune system possibly mediated by melanocortin receptors in skin adipocytes.^{11,12}

Glucocorticoids inhibits a broad range of T cell and B cell responses and exhibits potent suppressive effects on the effector functions of phagocytes. This makes them effective in controlling a wide range of inflammatory diseases but can also lead to adverse events as previously mentioned.^{1,13}

In this case the inherent hypercortisolic state of Cushing disease apparently suppressed the underlying sarcoidosis.

In conclusion we would like to highlight the risk of corticosteroid-responsive diseases following successful treatment of Cushing syndrome. We propose a prospective follow-up study to examine the incidence of

autoimmune and corticosteroid-responsive diseases after surgery.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Consent

Informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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